REMARKS/ARGUMENTS

This is in response to the Office Action mailed September 21, 2005 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Claims 1-3, 5, 12, 13, 16, 25, 26, 28-30 and 32 were examined.

The Examiner objected to the amendment filed September 8, 2003 as introducing new matter. In particular, the Examiner asserts that the amendment to refer to "bases including bases 336 to 663" in place of "amino acids 336 to 663" is new matter. Applicants respectfully disagree.

As a first matter, the phrase in the specification with amendments shown is

> the CD28 cytoplasmic domain (particularly a fragment encoded by bases including bases ~~spanning amino acids~~ 336 to 663 of CD28 cDNA)

Thus, the fragment referred to is necessarily a fragment of the CD28 cytoplasmic domain. The original term in the specification was "spanning." The ordinary meaning of this term is "going across." In other words, the original disclosure was to cover at least the numbers residues but did not exclude longer fragments. This is exactly the concept and scope that has been set forth in the amended specification, with words more appropriate to a nucleotide sequence. Thus, no new matter was added.

The Examiner objected to the specification because no sequence listing had been supplied. A sequence listing has been filed electronically. A printed copy of the sequence listing is attached, and Applicants request entry of this sequence listing at the appropriate location in the specification. The undersigned certifies that the electronic copy and the printed copy have the same content. Amendments to the specification have been made to add references to the sequence ID numbers.

Claims 5, 12, 25, 26 and 28 have been amended in accordance with the Examiner's comments and suggestions.

Claims 1, 12, 13 and 16 are rejected under 35 USC § 112, first paragraph for lack of written description. Applicants respectfully traverse this rejection. Recently, in *Capon v. Eshhar*, 76 USPQ2d 1078 (Fed. Cir. 2005), the Federal Circuit has considered an interference proceeding in which the Patent Office Board of Appeals found that neither applicant's disclosure met the written description requirement Both applications related to chimeric genes designed to combine DNA encoding known antigen-binding domains and known lymphocyte-receptor protein into a unitary gene. Both applications claims such chimeric genes generically. The

Patent Office Board of Appeals and Interferences held that there was a lack of written description because the applications claimed the invention in terms of function, instead of specific sequences or structures. The Federal Circuit vacated this holding, finding that the failure to explicitly present specific sequences based on known genes did not create a basis for a rejection for lack of written description, and stated that no *per se* rule exists for the recitation of specific sequences.

The case now before the Examiner is similar to *Capon*.[1] Like Capon, the claims recite constructs that are generically described based on function, and the actual bases of every known sequence or combination of sequences with the scope of the claims are not explicitly set forth. The nucleic constructs of *Capon* were not limited to known antibodies or receptor binding proteins, although constructs could be built from known sequences. This is the case in the present application as well.

In *Capon*, one disclosure provided specific sequences for 16 receptors and 4 sc-Fv, while the other relied on citations to literature sources. Neither included a sequence for a complete chimeric gene as claimed. The Federal Circuit found that this was sufficient to avoid any kind of *per se* ruling. In the present application, the only issue relates to the cytoplasmic domain component of the fusion protein. Applicants disclose multiple examples which, like the parts of the constructs in *Capon* are described functionally. Contrary to the Examiner's argument, this use of a functional characterization, is not grounds for a written description rejection.

For these reasons, Applicants submit that the rejection for lack of written description is in error and should be withdrawn.

The Examiner has rejected the claims under consideration as obvious over various new combinations of references. Each of these rejections share as a common basis a reliance on a combination of US Patent Publication 2003/0077249 or WO97/23613 in view of US Patent No. 5,538,866.

The Examiner argues that the claims are directed to a fusion protein comprising a single-chain scFv antibody to PSMA, a cytoplasmic domain cytoplasmic and optionally a connector. To avoid possible ambiguity, Applicants have amended claim 1 to delete the word "optional" since the previous amendment indicated that the connector hinge was present and the CD8 hinge.

The Examiner argues that the primary references teach a fusion protein comprising an scFv, a cytoplasmic domain and a CD hinge connector. The scFv of the primary references is not

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[1] In fact, one of the applications involved in the interference is the Eshhar reference previously cited in this case. Thus Capon is both legally and factually related.

targeted to PSMA. The Examiner cites US 5,538,866 as disclosing PSMA and that antibodies that bond to PSMA are therapeutically useful. Based on this, the Examiner argues that Applicants claimed invention would have been obvious. Applicants respectfully disagree.

In response to the prior Office Action, Application submitted a copy of a paper by Guest et al. that shows the selection of a particular combination of connector and scFv is necessary to achieve and/or optimize antibody activity.

In assessing obviousness as a legal concept, it is important to remember that the prior art must provide not merely a teaching of the elements of the claimed invention, but also a motivation to combine them with a reasonable expectation of success. Where the art is unpredictable, the teaching of the art should be more compelling in order to meet the second part of this standard. In the present case, this is true because the ability to make a given construct and the functional properties of that construct cannot be said to be generally predictable.

The selection of PSMA as a target antigen to be combined into the structures of the primary references is plainly guided in this case by the present claims. There is no specific motivation to select PSMA, as opposed to any other antigen of interest. Thus, the propriety of the rejection should be tested against a more general standard, whether making any and every fusion of the general type disclosed in the primary references became *prima facie* obvious as of the date of those references. Applicants submit that this is not the case.

As a first matter, Applicants point out that the art as it relates to fusion proteins with an antibody and a cytoplasmic domain is not limited to the primary references now cited. Other references have been cited earlier which offer teachings of other antibodies, without a CD8 connector. This means that fairly stated, claim 1 of this application is only reached of one skilled in the art makes a particular selection (PSMA) from the antibody column which fairly contains all known antibodies of therapeutic interest, and a particular selection from the connector column which contains multiple entries for combination with a cytoplasmic domain. As was the case in *In re Geiger,* at best "one skilled in the art might find it obvious to try various combinations of these known" antibodies and connectors. 12 USPQ2d 1276, 1278 (Fed. Cir. 1987). Obvious- to-try, however, this is not the standard of 35 U.S.C. § 103. *In re Goodwin*, 198 USPQ 1, 3 (CCPA 1978); *In re Antonie*,195 USPQ 6 (CCPA 1977); *In re Tomlinson*, 150 USPQ 623 (CCPA 1966).

Further, Applicants again submit that the Examiner has failed to properly take into account the characteristics of the claimed fusion proteins in assessing obviousness. As has been previously pointed out, biotechnology is a complex art, and the ability to make a given construct and the functional properties of that construct cannot be said to be generally predictable. In determining obviousness, however, the properties that are disclosed for the constructs of the art and the constructs of the invention must be taken into account, and any differences between these

properties is fair evidence of unobviousness. *See, In re Margolis*, 228 U.S.P.Q. 940 (Fed. Cir. 1986).

As noted in the present application, tests showing IL-2 stimulation, while suggestive of utility, are not dispositive since they may be followed by T cell anergy or apoptosis. This results in T cell death *in vivo* rather than the development of an appropriate immune response. (Page 3, lines 31-33; Page 14, lines 47) Insufficient costimulatory signals and perhaps other problems can render a composition effectively useless if the cells expressing the fusion does not remain alive, undergo proliferation and respond when a restimulation occurs. Art such as the Alternschmidt article (of record, cited on Page 14 of the present application) show that it may not be presumed for different antibodies than the one tested in Eshhar. In contrast, the present application does demonstrate this activity for PSMA-CD8 containing species. This is a patentable and unobvious advance over the art which teaches at best techniques, and not the claimed invention.

The additional art relied upon by the examiner offers nothing of specific relevance to the independent claim. For these reasons, Applicants submit that the rejections under 35 USC § 103 should be withdrawn.

Claims 1-3, 12, 13, 25, 26, 29 and 30 stand rejected for obviousness-type double patenting in view, and as not being patentably distinct from US Patent Application No. 10/448,256 in view of the now cited Bebbington art. Applicants traverse both these rejections.

Application Serial No. 10/448,256 claims priority to a provisional application filed May 28, 2002. This present application was published on March 16, 2000 as PCT Publication No. WO 00/14257. As such, the disclosure of the present application is prior art with respect to the cited application, and presumably claims will not issue in that case which are obvious over the disclosure of the present application.

Furthermore, the invention of the cited application is different from that now claimed. In the present application, the claims are directed to a fusion in which includes a cytoplasmic domain, such as the CD3 zeta-chain cytoplasmic domain **or** the CD28 cytoplasmic domain. The claims of the cited application are to a fusion that intracellular domain of the CD3 zeta chain **and** a costimulatory region such as the intracellular domain of CD28. The use of both cytoplasmic/intracellular portions as described in the cited invention is a distinct and patentable improvement over the disclosure of the present application. The fact that the claims of this application may dominate the later claims to some extent is not dispositive with respect to obviousness-type double patenting.

Furthermore, Applicants note that in the comments on the lack of distinctness, the Examiner indicates that the applications are commonly assigned. However, this application has two assignees, while the cited application has only one. Furthermore, since the cited application was filed later than this application, that application could not be prior art under any section of the statute. Thus, this rejection improper even if there were "conflicting subject matter" which there is not.

For these reasons, the elected claims are believed to be in form for allowance. Accordingly, recombination of the withdrawn claims related to unelected species and methods of using the fusion proteins and allowance of the application as a whole is hereby requested.

Respectfully Submitted,

Marina T. Larson, Ph.D
Attorney/Agent for Applicant(s)
Reg. No. 32038

(970) 468 6600

SEQUENCE LISTING

<110> Sadelain, Michel
Bander, Neil H
Gong, Michael

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